

A case of oral multiple primary cancer including Spindle Cell Carcinoma

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Abstract Spindle Cell Carcinoma (SPCC) is a relatively rare tumour that is classified as a subtype of squamous cell carcinoma (SCC). Histologically, SPCC is composed of a SCC region and epithelium-derived spindle cells with mesenchymal differentiation. We encountered an interesting case of multiple cancer including SPCC. A histopathologically atypical papillary lesion was found 13 years before our initial examination. Multiple verrucous leukoplakia later developed in the oral mucosa, for which an oral vitamin A derivative (a retinoid) was intermittently administered. Multiple cancer including SPCC subsequently developed in the lower gingiva. We investigated the case histologically and immunohistologically based on the concept of field cancerization.

Keywords Spindle cell carcinoma · Squamous cell carcinoma · Multiple cancer · Retinoid · Field cancerization

Introduction

Spindle cell carcinoma (SPCC) is a relatively rare tumour that is classified as a subtype of Squamous cell carcinoma

(SCC). Histologically, SPCC is composed of a SCC region and epithelium-derived spindle cells with mesenchymal differentiation [1]. Head and neck SPCC in the laryngeal region has been reported frequently [2, 3], but there are fewer cases in the gingiva [4]. Here, we describe an interesting case of multiple cancer including SPCC that developed in the lower gingiva.

Case Report

The patient was a 74-year-old Japanese woman who visited the Department of Oral and Maxillofacial Surgery, Mie University School of Medicine for a chief complaint of a mass in the median region of the lower lip. She had no history of cigarette smoking or habitual alcohol intake. A 7 mm papillary lesion with a clear boundary had appeared in the right lower gingiva 13 years before our initial examination and the lesion was excised, but no malignant findings were noted pathologically, although atypical changes were present. Later, multiple white patches including those of the verrucous type appeared in the oral mucosa (Fig. 1), but were not malignant on biopsy. Leukoplakia was diagnosed and the course was followed under treatment with 25–30 mg/day of a vitamin A retinoid derivative. The patient had stopped visiting the hospital 6 months before our initial examination. However, she was referred by a physician to our department.

The patient was tall and well-built. Her facial complexion was laterally asymmetric, and a 23 × 15 mm elastic, soft mass with a relatively clear boundary was present in the median region of the lower lip. The surface of the mass was rough and blackish (Fig. 2). No abnormality was noted in the regional lymph nodes.

On MRI, a 21 × 15 × 21 mm lesion showing low and high signals on T1 and T2 weighted images, respectively,

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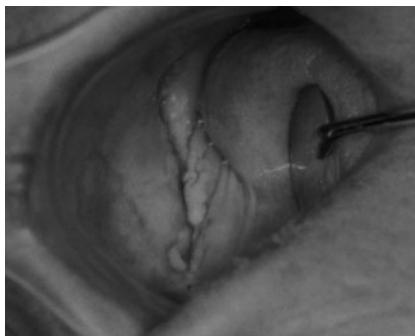


Fig. 1 Verrucous leukoplakia had appeared in the right lower gingiva



Fig. 2 The oral cavity at the initial examination. A mass with a relatively clear boundary in the median region of the lower lip

was noted in the lower lip, but there were no findings suggesting lingual or mandibular invasion. On PET-CT, accumulation with an SUV value of 5.4 was found in the lower lip, with no abnormal accumulation in other regions. On biopsy, cells containing atypical nuclei accompanied by keratinization were enlarged to various sizes and had proliferated and infiltrated in a sheet-like arrangement, based on which well-differentiated SCC was diagnosed (T2N0M0) (Fig. 3). Chemotherapy (CDDP: 85 mg, PEP: 5 mg/day, 25 mg in total) and LINAC radiotherapy (2 Gy/day × 35 times, 70 Gy in total) were performed. The tumour disappeared macroscopically and no residual malignant tumour cells were present on biopsy.

After discharge, the patient was followed at the outpatient clinic, but a 4 × 31 mm ulcer formed in the gingiva of the upper median region and an 11 × 30 mm erosive lesion developed in the right lower gingiva. Histopathological diagnosis indicated that the lesion in the upper median region was intraepithelial cancer and that in the right lower lesion was moderately differentiated SCC (upper median lesion: T2N0M0, right lower lesion: T2N0M0). Since there were no findings suggesting regional lymph node metastasis on CT or MRI, chemotherapy (PEP: 5 mg/day, 25 mg in total, MMC: 6 mg) was performed, followed by tumour resection. The postoperative course was favorable and the

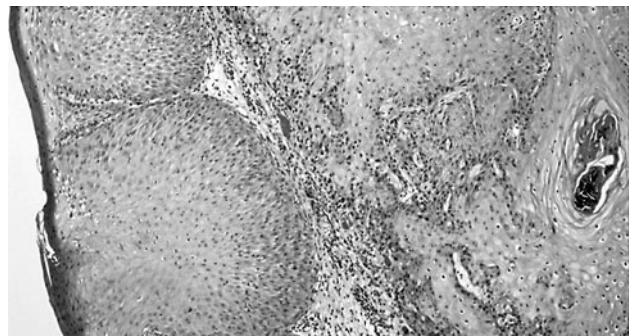


Fig. 3 Histopathological view. Showing cells containing atypical nuclei accompanied by keratinization with proliferation and infiltration in a sheet-like arrangement. HE staining ×75



Fig. 4 The oral cavity 2 years and 7 months after the initial examination. It was revealed a cauliflower-shaped mass in the left lower gingiva

patient was again followed at the outpatient clinic. However, a papillary lesion with a diameter of 3 mm developed in the right margin of the tongue 1 year after the initial examination, and a 20 × 20 mm mass formed in the gingiva of the lower median region in the following month. The whole lesions were excised for biopsy. Since both lesions showed only atypical changes on histopathological examination, the lesions were subjected to course observation, but an 18 × 15 mm cauliflower-shaped mass developed in the left lower gingiva 2 years and 7 months after the initial examination (Fig. 4). Biopsy was performed and the mass was histopathologically diagnosed as poorly differentiated SCC (T1N0M0).

The patient was admitted to the hospital and underwent removal of tumour. On postoperative histopathological examination, infiltrating and proliferating well-differentiated SCC components with an alveolar, funicular structure accompanied by horn pearls and a region consisting of proliferating spindle, polygonal, and epithelioid-like atypical cells were present, with some regions showing transitional features between the two types. Immunohistochemically, the spindle cells were positive for CK-pan vimentin and negative

Table 1 Immunohistochemical staining

Antibody	Result
pan-CK	+
Vimentin	+
EMA	–
α-SMA	–

for EMA and α-SMA (Table 1). Based on these findings, SPCC was diagnosed (Fig. 5). Since postoperative MRI suggested left submandibular lymph node metastasis (Fig. 6), and middle and posterior submandibular lymph node metastasis was found in a pathological examination, left cervical lymph node dissection was performed. A postoperative pathological examination showed metastases from SPCC to the superior internal deep cervical and submental lymph nodes. The tumour subsequently recurred in the mental region and radiotherapy was performed (0.8 Gy/day, 50.4 Gy in total), but tumour enlargement continued and the patient died 3 years after the initial examination. No pathological autopsy was performed.

Discussion

SPCC is a relatively rare disease that is positioned as a subtype of SCC in the histological classification of head and neck tumours established by the WHO in 2005, and characterized by the concomitant presence of cancer and epithelium-derived spindle cells with mesenchymal differentiation [1]. The larynx is the most frequent site of development in the head and neck region. In the oral cavity, many cases of SPCC in the lips and tongue have been reported, but development of SPCC in the alveolar gingiva is relatively rare [4–7]. SPCC tends to occur more frequently in men and the onset age varies from the 20s to

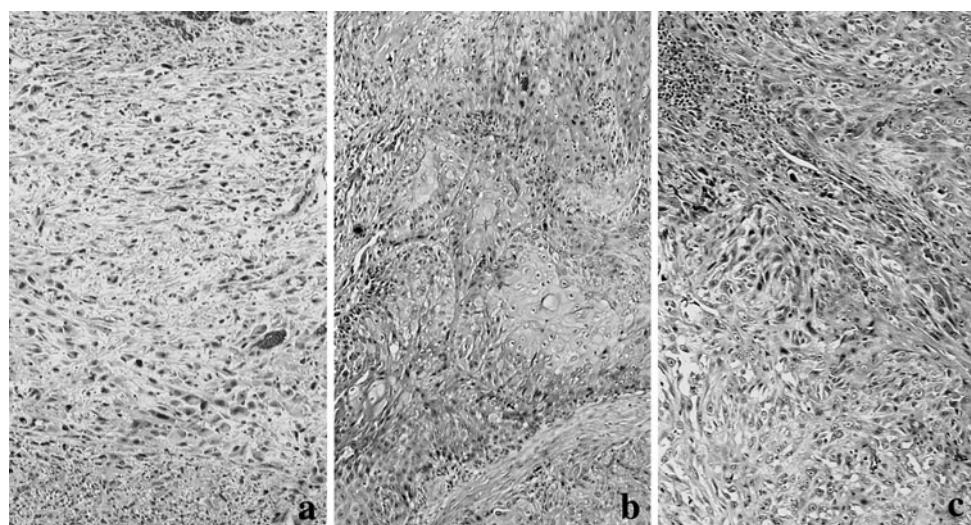
the 90s, with a reported association with cigarette smoking and alcohol consumption [2, 4–6, 8, 9]. Lesions show polyp-like or sessile outward growth, have a mean size of 18–20 mm, and exhibit symptoms of swelling, pain, and refractory ulcer in many cases [2, 4, 6, 8].

The prognosis of SPCC is poorer than that of general SCC, and metastasis also occurs in many cases, particularly in the cervical lymph node, lung, and heart. Ellis et al. [4] reported metastasis in 16 of 59 cases, with 11 occurrences in the cervical lymph node, and Su et al. [5] found a metastasis rate of 33.3%. Survival rates for SPCC of 36% [4] and 27.5% [5] have been reported. SPCC is treated similarly to SCC through surgery alone or in combination with radiotherapy, but high recurrence rates after treatment of 12 of 59 cases [4] and 73.3% [5] have been reported.

Histologically, SPCC consists of SCC and a component reflecting mesenchymal differentiation. A partial transitional region is apparent in some cases. In our patient, atypical spindle cell proliferation was continuous from the well-differentiated squamous cell carcinoma component. Since only spindle cells may be present in a small biopsied tissue specimen, differentiation from non-epithelial tumours such as fibrosarcoma, synovial sarcoma, leiomyosarcoma, and malignant fibrous histiocytoma is necessary [2, 9]. Because the incidence of sarcoma in the oral cavity is generally low, SPCC should also be suspected when only spindle cells are present, and re-investigation by sampling of a relatively large specimen is important.

Regarding the histological origin of SPCC, in many cases spindle cells are positive for a mesenchymal cell marker, vimentin, and simultaneously positive for epithelial cell markers such as cytokeratin on immunohistochemical staining, suggesting that the tumour is formed by mesenchymal differentiation of epithelium-derived cells. CK-pan and vimentin were positive and EMA and α-SMA were negative in our patient, based on which spindle cell

Fig. 5 Histopathological view. Showing a sarcoma-like region consisting of proliferative atypical spindle cells (a), well-differentiated squamous cell carcinoma with infiltration and proliferation accompanied by cancer pearls (b), and a partial transitional region (c). HE staining $\times 100$



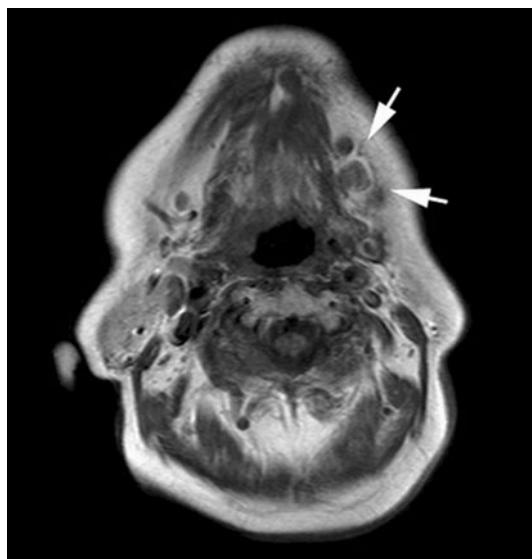


Fig. 6 MR image. Suggesting left submandibular lymph node metastasis

carcinoma was diagnosed. Iguchi et al. [9] reported a case in which SPCC developed as a recurrent tumour following surgery for SCC, suggesting a relationship with radiotherapy. In our patient, radiotherapy and chemotherapy were performed before development of SPCC and these therapies may have promoted an anaplastic change from SCC to SPCC.

Proliferative verrucous leukoplakia (PVL) was first reported by Hansen et al. [10] in 1985. PVL is associated with repeat hyperplasia, multiple development, and recurrence, and often becomes malignant over a long course. In our patient, an atypic papillary lesion was noted 13 years before our initial examination, and multiple leukoplakia including the verrucous type later developed and became malignant. This suggests a diagnosis of PVL. More than 150 cases of PVL have been reported [10–16] and the rate of malignant conversion during the disease course is higher than 70% [11]. Malignant conversion to SCC and verrucous carcinoma (VC) has been reported [10–16], but there has been no case of conversion of PVL with an anaplastic change to SPCC. Thus, the present case provides the first example of such a course of PVL.

Warren and Gates [17] defined multiple cancer as tumours with specific malignant features that arise at different distant sites and are not caused by metastasis from each other. The presence of several cancers in the same organ is defined as multiple cancer, and a similar presence in two or more organs as multiple primary cancer. In the Surveillance, Epidemiology and End Results (SEER) manual [18], multiple cancer with an interval between diagnoses of the initial and late tumours of less than 2 months is defined as synchronous, and that with an interval between diagnoses exceeding 2 months as

metachronous. In our patient, SCC and SPCC in different stages of differentiation were found in the lower lip and upper and lower alveolar regions at intervals of 6 and 19 months, respectively, and therefore this case is classified as metachronous multiple cancer.

Development of multiple cancer is commonly associated with the concept of field cancerization, in which several tumours develop at different distant sites due to gene aberration induced by carcinogens such as alcohol and cigarettes, but not by metastasis of tumour cells [19]. However, our patient had no history of alcohol consumption or cigarette smoking, and no particular familial medical history. Therefore, radiotherapy, chemotherapy, and particularly oral vitamin A derivative treatment for oral mucosal dysplasia may have been involved in development of the multiple cancer. Vitamin A derivatives (retinoids) administered to prevent cancerization of leukoplakia showing dysplasia and to inhibit cancer cell proliferation such as that in prostate cancer and hepatocellular carcinoma are teratogenic drugs. Retinoids regulate cell growth, differentiation, and proliferation through induction of formation of heterodimers of the retinoic acid receptor-g (RAR-g) and retinoid X receptor-a (RXR-a), which then control gene expression by binding to a target promoter [20]. The retinoid receptors may interfere with signal transmission through the transcriptional regulator AP-1, and deregulation of AP-1 is associated with malignant transformation and inflammatory diseases [20]. The patient had taken a retinoid (Tigason) intermittently for about 14 years from 12 years before our initial examination, and this drug may have altered gene expression in oral tissue and affected cell differentiation, resulting in development of multiple oral cancers and a subsequent transition from SCC to SPCC.

Malignant conversion to SCC resulting from administration of vitamin A derivatives (retinoids) in PVL patients has been reported previously [12, 13]. Thus, although retinoids are useful drugs for treatment of keratinizing lesions such as leukoplakia, these drugs should be administered carefully based on the possible development of multiple cancer in cases requiring long-term treatment for multiple leukoplakia, and particularly in cases of PVL. To prevent field cancerization, habitual ingestion of carcinogens such as alcohol and cigarettes should be stopped, and long-term follow-up may be needed for patients treated with radiotherapy, chemotherapy, and teratogenic drugs such as retinoids.

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